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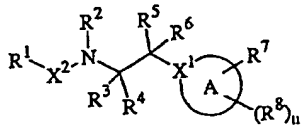
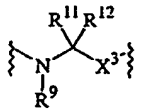
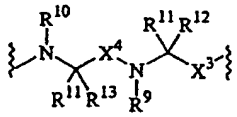
(54) Title: AMINE DERIVATIVES AS PROTEASE INHIBITORS



(I)



(a)



(b)

(57) Abstract

The present invention relates to novel alkanoyl–substituted heterocyclic derivatives which are cysteine protease inhibitors; the pharmaceutically acceptable salts and *N*–oxides thereof; their uses as therapeutic agents and the methods of their making; according to Formula (I) in which: A comprises a heteromonocyclic ring containing 5 to 6 ring member atoms or a fused heteropolycyclic ring system containing 8 to 14 ring member atoms, wherein each ring contains 5 to 7 ring member atoms, X^1 is a ring member carbon atom and each ring member atom other than X^1 is a carbon atom or a heteroatom, with the proviso that (i) at least one ring member atom is a heteroatom and (ii) when A is a heteromonocyclic radical containing 5 ring member atoms, no more than two of the ring member atoms comprising A are heteroatoms; n is 0, 1, 2 or 3; X^1 is =C– or –CH–; X^2 is a bond or a divalent group of Formula (a) or (b); R^1 – R^8 = as in the application.

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AMINE DERIVATIVES AS PROTEASE INHIBITORS

THE INVENTION

This application relates to compounds and compositions for treating diseases associated with cysteine protease activity, particularly diseases associated with activity of cathepsins B, K, L or S.

DESCRIPTION OF THE FIELD

Cysteine proteases represent a class of peptidases characterized by the presence of a cysteine residue in the catalytic site of the enzyme. Cysteine proteases are associated with the normal degradation and processing of proteins. The aberrant activity of cysteine proteases, e.g. as a result of increased expression or enhanced activation, however, may have pathological consequences. In this regard, certain cysteine proteases are associated with a number of disease states, including arthritis, muscular dystrophy, inflammation, tumor invasion, glomerulonephritis, malaria, periodontal disease, metachromatic leukodystrophy and others. For example, increased cathepsin B levels and redistribution of the enzyme are found in tumors; thus, suggesting a role for the enzyme in tumor invasion and metastasis. In addition, aberrant cathepsin B activity is implicated in such disease states as rheumatoid arthritis, osteo arthritis, pneumocystis carinii, acute pancreatitis, inflammatory airway disease and bone and joint disorders.

The prominent expression of cathepsin K in osteoclasts and osteoclast-related multinucleated cells and its high collagenolytic activity suggest that the enzyme is involved in ososteoclast-mediated bone resorption and, hence, in bone abnormalities such as occurs in osteoporosis. In addition, cathepsin K expression in the lung and its elastinolytic activity suggest that the enzyme plays a role in pulmonary disorders as well.

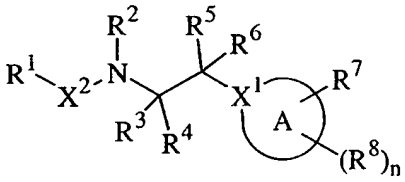
Cathepsin L is implicated in normal lysosomal proteolysis as well as several disease states, including, but not limited to, metastasis of melanomas. Cathepsin S is implicated in Alzheimer's disease and certain autoimmune disorders, including, but not limited to juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythemotasus, rheumatoid arthritis and Hashimoto's thyroiditis; allergic

disorders, including, but not limited to asthma; and allogeneic immune responses, including, but not limited to, rejection of organ transplants or tissue grafts.

In view of the number of diseases wherein it is recognized that an increase in cysteine protease activity contributes to the pathology and/or symptomatology of the disease, molecules which are shown to inhibit the activity of this class of enzymes, in particular molecules which are inhibitors of cathepsins B, K, L and/or S, will be useful as therapeutic agents.

SUMMARY OF THE INVENTION

In one particular embodiment, the present invention relates to protease inhibitors of Formula I:



I

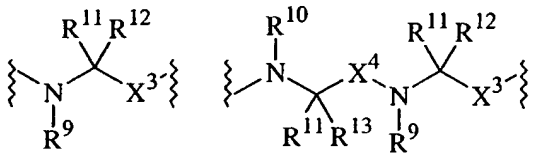
in which:

A comprises a heteromonocyclic ring containing 5 to 6 ring member atoms or a fused heteropolycyclic ring system containing 8 to 14 ring member atoms, wherein each ring contains 5 to 7 ring member atoms, X^1 is a ring member carbon atom and each ring member atom other than X^1 is a carbon atom or a heteroatom, with the proviso that (i) at least one ring member atom is a heteroatom and (ii) when A is a heteromonocyclic radical containing 5 ring member atoms, no more than two of the ring member atoms comprising A are heteroatoms;

n is 0, 1, 2 or 3;

X^1 is =C- or -CH-;

X^2 is a bond or a divalent group of Formula (a) or (b):



(a) (b)

wherein:

X^3 and X^4 independently are -C(O)- or $-CH_2S(O)_2-$

R^9 and R^{10} independently are hydrogen, (C_{1-6})alkyl or as defined below;

R^{11} at each occurrence independently is hydrogen or (C_{1-6})alkyl;

R^{12} and R^{13} independently are (i) (C_{1-6})alkyl optionally substituted with cyano, halo, nitro, $-NR^{14}R^{14}$, $-NR^{14}C(O)OR^{14}$, $-NR^{14}C(O)NR^{14}R^{14}$, $-NR^{14}C(NR^{14})NR^{14}R^{14}$, $-OR^{14}$, $-SR^{14}$, $-C(O)OR^{14}$, $-C(O)NR^{14}R^{14}$, $-S(O)_2NR^{14}R^{14}$, $-P(O)(OR^{14})OR^{14}$, $-OP(O)(OR^{14})OR^{14}$, $-NR^{14}C(O)R^{15}$, $-S(O)R^{15}$, $-S(O)_2R^{15}$, $-C(O)R^{15}$, $-OR^{16}$, $-SR^{16}$, $-S(O)R^{16}$, $-S(O)_2R^{16}$, $-C(O)R^{16}$, $-C(O)OR^{16}$, $-OC(O)R^{16}$, $-NR^{16}R^{17}$, $-NR^{17}C(O)R^{16}$, $-NR^{17}C(O)OR^{16}$, $-C(O)NR^{16}R^{17}$, $-S(O)_2NR^{16}R^{17}$, $-NR^{17}C(O)NR^{16}R^{17}$ or $-NR^{17}C(NR^{17})NR^{16}R^{17}$, wherein R^{14} at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl, R^{15} is (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl, halo, (C_{1-6})alkyl or R^{16} is (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl, (C_{9-12})polycycloaryl(C_{0-6})alkyl or hetero(C_{8-12})polycycloaryl(C_{0-6})alkyl and R^{17} is hydrogen or (C_{1-6})alkyl, and wherein within R^{16} said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, polycycloaryl or heterpolycycloaryl ring optionally is substituted by a group selected from $-R^{18}$, $-X^5OR^{18}$, $-X^5SR^{18}$, $-X^5S(O)R^{18}$, $-X^5S(O)_2R^{18}$, $-X^5C(O)R^{18}$, $-X^5C(O)OR^{18}$, $-X^5OC(O)R^{18}$, $-X^5NR^{18}R^{19}$, $-X^5NR^{19}C(O)R^{18}$, $-X^5NR^{19}C(O)OR^{18}$, $-X^5C(O)NR^{18}R^{19}$, $-X^5S(O)_2NR^{18}R^{19}$, $-X^5NR^{19}C(O)NR^{18}R^{19}$ or $-X^5NR^{19}C(NR^{19})NR^{18}R^{19}$, wherein X^5 is a bond or (C_{1-6})alkylene, R^{18} is hydrogen or (C_{1-6})alkyl and R^{19} is (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl, (C_{9-12})polycycloaryl(C_{0-6})alkyl or hetero(C_{8-12})polycycloaryl(C_{0-6})alkyl, or (ii) a group selected from (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl, (C_{9-12})polycycloaryl(C_{0-6})alkyl and hetero(C_{8-12})polycycloaryl(C_{0-6})alkyl, wherein said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, polycycloaryl or heterpolycycloaryl ring optionally is substituted by a group selected from $-R^{18}$, $-X^5OR^{18}$, $-X^5SR^{18}$, $-X^5S(O)R^{18}$, $-X^5S(O)_2R^{18}$, $-X^5C(O)R^{18}$, $-X^5C(O)OR^{18}$, $-X^5OC(O)R^{18}$, $-X^5NR^{18}R^{19}$, $-X^5NR^{19}C(O)R^{18}$, $-X^5NR^{19}C(O)OR^{18}$, $-X^5C(O)NR^{18}R^{19}$, $-X^5S(O)_2NR^{18}R^{19}$, $-X^5NR^{19}C(O)NR^{18}R^{19}$ or $-X^5NR^{19}C(NR^{19})NR^{18}R^{19}$, wherein X^5, R^{18} and R^{19} are as defined above; wherein within R^{12} and/or R^{13} any alicyclic or aromatic ring system present may be substituted

further by 1 to 5 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted (C_{1-4})alkyl, nitro, $-X^5NR^{14}R^{14}$, $-X^5NR^{14}C(O)OR^{14}$, $-X^5NR^{14}C(O)NR^{14}R^{14}$, $-X^5NR^{14}C(NR^{14})NR^{14}R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{14}$, $-X^5S(O)_2NR^{14}R^{14}$, $-X^5P(O)(OR^{14})OR^{14}$, $-X^5OP(O)(OR^{14})OR^{14}$, $-X^5NR^{14}C(O)R^{15}$, $-X^5S(O)R^{15}$, $-X^5S(O)_2R^{15}$ and $-X^5C(O)R^{15}$, wherein X^5, R^{14} and R^{15} are as defined above; or

R^{12} together with R^9 and/or R^{13} together with R^{10} form trimethylene, tetramethylene or phenylene-1,2-dimethylene, optionally substituted with 1 to 3 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted (C_{1-4})alkyl, nitro, oxo, $-X^5NR^{14}C(O)OR^{14}$, $-X^5NR^{14}C(O)NR^{14}R^{14}$, $-X^5NR^{14}C(NR^{14})NR^{14}R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{14}$, $-X^5S(O)_2NR^{14}R^{14}$, $-X^5P(O)(OR^{14})OR^{14}$, $-X^5OP(O)(OR^{14})OR^{14}$, $-X^5NR^{14}C(O)R^{15}$, $-X^5S(O)R^{15}$, $-X^5S(O)_2R^{15}$ and $-X^5C(O)R^{15}$, wherein X^5, R^{14} and R^{15} are as defined above; and

R^1 is $-X^6X^7R^{20}$, wherein X^6 is -C(O)-, -C(O)C(O)- or $-S(O)_2-$, X^7 is a bond, -O- or $-NR^{21}-$, wherein R^{21} is hydrogen or (C_{1-6})alkyl, and R^{20} is (i) (C_{1-6})alkyl optionally substituted by cyano, halo, nitro, $-NR^{14}R^{14}$, $-NR^{14}C(O)OR^{14}$, $-NR^{14}C(O)NR^{14}R^{14}$, $-NR^{14}C(NR^{14})NR^{14}R^{14}$, $-OR^{14}$, $-SR^{14}$, $-C(O)OR^{14}$, $-C(O)NR^{14}R^{14}$, $-S(O)_2NR^{14}R^{14}$, $-P(O)(OR^{14})OR^{14}$, $-OP(O)(OR^{14})OR^{14}$, $-NR^{14}C(O)R^{15}$, $-S(O)R^{15}$, $-S(O)_2R^{15}$, $-C(O)R^{15}$, $-OR^{22}$, $-SR^{22}$, $-S(O)R^{22}$, $-S(O)_2R^{22}$, $-C(O)R^{22}$, $-C(O)OR^{22}$, $-C(O)NR^{22}R^{23}$, $-NR^{22}R^{23}$, $-NR^{23}C(O)R^{22}$, $-NR^{23}C(O)OR^{22}$, $-NR^{23}C(O)NR^{22}R^{23}$ or $-NR^{23}C(NR^{23})NR^{22}R^{23}$, wherein R^{14} and R^{15} are as defined above, R^{22} is (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl, (C_{9-12})bicycloaryl(C_{0-6})alkyl or hetero(C_{8-12})bicycloaryl(C_{0-6})alkyl and R^{23} at each occurrence independently is hydrogen or (C_{1-6})alkyl, or

(ii) (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl, (C_{9-12})bicycloaryl(C_{0-6})alkyl or hetero(C_{8-12})bicycloaryl(C_{0-6})alkyl or (iii) (C_{3-6})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-6})cycloalkyl(C_{0-6})alkyl, phenyl(C_{0-6})alkyl or hetero(C_{5-6})aryl(C_{0-6})alkyl, wherein said cycloalkyl, heterocycloalkyl, phenyl or heteroaryl is substituted by $-R^{24}$, $-X^5OR^{24}$, $-X^5SR^{24}$, $-X^5S(O)R^{24}$, $-X^5S(O)_2R^{24}$, $-X^5C(O)R^{24}$, $-X^5C(O)OR^{24}$, $-X^5C(O)NR^{24}R^{25}$, $-X^5NR^{24}R^{25}$, $-X^5NR^{25}C(O)R^{24}$, $-X^5NR^{25}C(O)OR^{24}$, $-X^5NR^{25}C(O)NR^{24}R^{25}$ or $-X^5NR^{25}C(NR^{25})NR^{24}R^{25}$, wherein X^5 is as defined above, R^{24} is (C_{3-6})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-6})cycloalkyl(C_{0-6})alkyl, phenyl(C_{0-6})alkyl or hetero(C_{5-6})aryl(C_{0-6})alkyl and R^{25} at each

occurrence independently is hydrogen or (C_{1-6})alkyl; wherein within R^1 any alicyclic or aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted (C_{1-4})alkyl, nitro, $-X^5NR^{14}R^{14}$, $-X^5NR^{14}C(O)OR^{14}$, $-X^5NR^{14}C(O)NR^{14}R^{14}$, $-X^5NR^{14}C(NR^{14})NR^{14}R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{14}$, $-X^5S(O)_2NR^{14}R^{14}$, $-X^5P(O)(OR^{14})OR^{14}$, $-X^5OP(O)(OR^{14})OR^{14}$, $-X^5NR^{14}C(O)R^{15}$, $-X^5S(O)R^{15}$, $-X^5S(O)_2R^{15}$ and $-X^5C(O)R^{15}$, wherein X^5, R^{14} and R^{15} are as defined above; or when X^2 is a divalent group of formula (a) or (b) then R^1 may also represent hydrogen, carboxy, oxalo or carbamoyl;

R^2 is hydrogen or (C_{1-6})alkyl;

R^3 is (i) (C_{1-6})alkyl optionally substituted with cyano, halo, nitro, $-SR^{26}$, $-C(O)OR^{26}$, $-C(O)NR^{26}R^{26}$, $-P(O)(OR^{26})OR^{26}$, $-OP(O)(OR^{26})OR^{26}$, $-S(O)R^{27}$, $-S(O)_2R^{27}$ or $-C(O)R^{27}$, wherein R^{26} at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl and R^{27} is (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl, or (ii) (C_{5-6})cycloalkyl(C_{2-3})alkyl, hetero(C_{3-6})cycloalkyl(C_{2-3})alkyl, (C_{6-12})aryl(C_{2-3})alkyl or hetero(C_{5-6})aryl(C_{2-3})alkyl, wherein said cycloalkyl, heterocycloalkyl, aryl or heteroaryl optionally is substituted further with 1 to 5 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted (C_{1-4})alkyl, nitro, $-X^5NR^{14}C(O)OR^{14}$, $-X^5NR^{14}C(O)NR^{14}R^{14}$, $-X^5NR^{14}C(NR^{14})NR^{14}R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{14}$, $-X^5S(O)_2NR^{14}R^{14}$, $-X^5P(O)(OR^{14})OR^{14}$, $-X^5OP(O)(OR^{14})OR^{14}$, $-X^5NR^{14}C(O)R^{15}$, $-X^5S(O)R^{15}$, $-X^5S(O)_2R^{15}$ and $-X^5C(O)R^{15}$, wherein X^5, R^{14} and R^{15} are as defined above, provided that when R^3 is unsubstituted (C_{1-5})alkyl and R^4 is hydrogen or unsubstituted (C_{1-5})alkyl, then X^2 may not represent (i) a bond when R^1 is $-C(O)R^{20}$, $-C(O)_2R^{20}$ or $-S(O)_2R^{20}$ in which R^{20} is (C_{1-6})alkyl, phenyl(C_{1-4})alkyl, phenyl, (C_{3-7})cycloalkyl, camphan-10-yl, naphth-1-yl, naphth-2-yl, phenyl substituted by one or more of (C_{1-4})alkyl, perfluoro(C_{1-4})alkyl, (C_{1-4})alkoxy, hydroxy, halo, amido, nitro, amino, (C_{1-4})alkylamino, (C_{1-4})dialkylamino, carboxy or (C_{1-4})alkoxycarbonyl, or naphth-1-yl or naphth-2-yl substituted by one or more of (C_{1-4})alkyl, perfluoro(C_{1-4})alkyl, (C_{1-4})alkoxy, hydroxy, halo, amido, nitro, amino, carboxy or (C_{1-4})alkoxycarbonyl or (ii) a divalent group of formula (a) or (b) in which the moiety R^{12} is methyl, isopropyl, *n*-butyl, *sec*-butyl, *tert*-butyl, 1-methylpropyl, benzyl, naphth-1-ylmethyl, naphth-2-ylmethyl, thien-2-ylmethyl, thien-3-ylmethyl, or wherein R^9 and R^{12} form ethylene, trimethylene, hydroxy-substituted trimethylene, tetramethylene or phenylene-1,2-dimethylene; or

R^3 and R^4 taken together with the carbon atom to which both R^3 and R^4 are attached

form (C_{3-8})cycloalkylene or (C_{3-8})heterocycloalkylene, wherein said cycloalkylene or heterocycloalkylene is optionally substituted with 1 to 3 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted (C_{1-4})alkyl, nitro, $-X^5NR^{14}C(O)OR^{14}$, $-X^5NR^{14}C(O)NR^{14}R^{14}$, $-X^5NR^{14}C(NR^{14})NR^{14}R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{14}$, $-X^5S(O)_2NR^{14}R^{14}$, $-X^5P(O)(OR^{14})OR^{14}$, $-X^5OP(O)(OR^{14})OR^{14}$, $-X^5NR^{14}C(O)R^{15}$, $-X^5S(O)R^{15}$, $-X^5S(O)_2R^{15}$ and $-X^5C(O)R^{15}$, wherein X^5, R^{14} and R^{15} are as defined above;

R^4 is hydrogen, (C_{1-6})alkyl or as defined above;

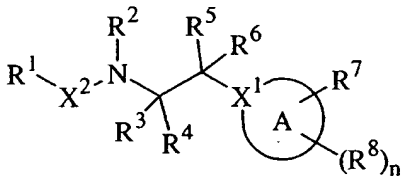
R^5 is hydrogen and R^6 is hydroxy or R^5 and R^6 together form oxo;

R^7 is a group selected from cyano, halo, nitro, $-R^{29}$, $-X^5NR^{29}R^{30}$, $-X^5NR^{30}C(O)OR^{29}$, $-X^5NR^{30}C(O)NR^{29}R^{30}$, $-X^5NR^{30}C(NR^{30})NR^{29}R^{30}$, $-X^5OR^{29}$, $-X^5SR^{29}$, $-X^5C(O)OR^{29}$, $-X^5C(O)NR^{29}R^{30}$, $-X^5S(O)_2NR^{29}R^{30}$, $-X^5P(O)(OR^{30})OR^{29}$, $-X^5OP(O)(OR^{29})OR^{29}$, $-X^5NR^{30}C(O)R^{31}$, $-X^5S(O)R^{31}$, $-X^5S(O)_2R^{31}$ and $-X^5C(O)R^{31}$, wherein X^5 is as defined above, R^{29} is hydrogen or $-R^{31}$, R^{30} at each occurrence is hydrogen or (C_{1-6})alkyl and R^{31} is (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl or hetero(C_{5-12})aryl(C_{0-6})alkyl, wherein within R^7 any alicyclic or aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted (C_{1-4})alkyl, nitro, $-X^5NR^{14}R^{14}$, $-X^5NR^{14}C(O)OR^{14}$, $-X^5NR^{14}C(O)NR^{14}R^{14}$, $-X^5NR^{14}C(NR^{14})NR^{14}R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{14}$, $-X^5S(O)_2NR^{14}R^{14}$, $-X^5P(O)(OR^{14})OR^{14}$, $-X^5OP(O)(OR^{14})OR^{14}$, $-X^5NR^{14}C(O)R^{15}$, $-X^5S(O)R^{15}$, $-X^5S(O)_2R^{15}$ and $-X^5C(O)R^{15}$, wherein X^5, R^{14} and R^{15} are as defined above; and

R^8 at each occurrence independently is selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted (C_{1-4})alkyl, nitro, $-X^5NR^{14}R^{14}$, $-X^5NR^{14}C(O)OR^{14}$, $-X^5NR^{14}C(O)NR^{14}R^{14}$, $-X^5NR^{14}C(NR^{14})NR^{14}R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{14}$, $-X^5S(O)_2NR^{14}R^{14}$, $-X^5P(O)(OR^{14})OR^{14}$, $-X^5OP(O)(OR^{14})OR^{14}$, $-X^5NR^{14}C(O)R^{15}$, $-X^5S(O)R^{15}$, $-X^5S(O)_2R^{15}$ and $-X^5C(O)R^{15}$, wherein X^5, R^{14} and R^{15} are as defined above; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.; but excluding compounds selected from the group consisting of ((S)-1-{(S)-1-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-3-methyl-butylcarbamoyl]-3-methyl-butylcarbamoyl}-3-methyl-butyl)-carbamic acid benzyl ester, {1-[1-(1-1*H*-imidazol-2-yl-

methanoyl)-3-methyl-butylcarbamoyl]-3-methyl-butyl}-carbamic acid *tert*-butyl ester, [(S)-3-methyl-1-((S)-3-methyl-1-{1-[1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-methanoyl}-butylcarbamoyl)-butyl]-carbamic acid benzyl ester; {(S)-1-[(S)-1-(1-1*H*-imidazol-2-yl-methanoyl)-3-methyl-butylcarbamoyl]-3-methyl-butyl}-carbamic acid benzyl ester, ((S)-1-{(S)-1-[1-(1-benzyl-1*H*-imidazol-2-yl)-methanoyl]-3-methyl-butylcarbamoyl}-3-methyl-butyl)-carbamic acid benzyl ester, {(S)-1-[(S)-1-(1-1*H*-imidazol-2-yl-methanoyl)-3-methyl-butylcarbamoyl]-3-methyl-butyl}-carbamic acid *tert*-butyl ester, 3-{[1-(4-chloro-phenyl)-methanoyl]-amino}-4-oxo-4-pyridin-3-yl-butyric acid ethyl ester, 4-furan-2-yl-4-oxo-3-{[1-(4-trifluoromethyl-phenyl)-methanoyl]-amino}-butyric acid ethyl ester, 3-(2-methyl-propanoylamino)-4-oxo-4-thiophen-2-yl-butyric acid ethyl ester, 4-oxo-4-thiophen-2-yl-3-[(1-*p*-tolyl-methanoyl)-amino]-butyric acid ethyl ester, 4-(5-bromo-thiophen-2-yl)-3-{[1-(4-chloro-phenyl)-methanoyl]-amino}-4-oxo-butyric acid ethyl ester, 3-{[1-(4-chloro-phenyl)-methanoyl]-amino}-4-(5-methyl-thiophen-2-yl)-4-oxo-butyric acid ethyl ester, 4-oxo-4-thiophen-3-yl-3-[(1-*p*-tolyl-methanoyl)-amino]-butyric acid ethyl ester, 3-{[1-(4-methoxy-phenyl)-methanoyl]-amino}-4-oxo-4-thiophen-3-yl-butyric acid ethyl ester, 3-{[1-(3,4-dichloro-phenyl)-methanoyl]-amino}-4-oxo-4-thiophen-3-yl-butyric acid ethyl ester, 4-fluoro-*N*-[1-(1-thiophen-3-yl-methanoyl)-propyl]-benzamide, 4-{[1-(4-fluoro-phenyl)-methanoyl]-amino}-5-oxo-5-thiophen-3-yl-pentanoic acid ethyl ester and 3-{[1-(4-fluoro-phenyl)-methanoyl]-amino}-2-methyl-4-oxo-4-thiophen-3-yl-butyric acid ethyl ester.

In another particular embodiment, the present invention relates to protease inhibitors of Formula I:



I

in which:

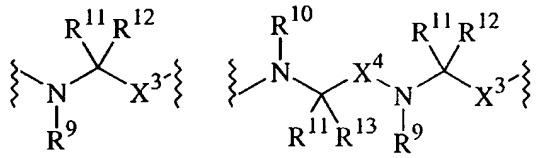
A comprises a heteromonocyclic ring containing 5 to 6 ring member atoms or a fused heteropolycyclic ring system containing 8 to 14 ring member atoms, wherein each ring contains 5 to 7 ring member atoms, X^1 is a ring member carbon atom and each ring member atom other than X^1 is a carbon atom or a heteroatom, with the proviso that (i) at least one ring member

atom is a heteroatom and (ii) when A is a heteromonocyclic radical containing 5 ring member atoms, no more than two of the ring member atoms comprising A are heteroatoms;

n is 0, 1, 2 or 3;

X^1 is =C- or -CH-;

X^2 is a bond or a divalent group of Formula (a) or (b):



(a) (b)

wherein:

X^3 and X^4 independently are -C(O)- or $-CH_2S(O)_2-$;

R^9 and R^{10} independently are hydrogen, (C_{1-6})alkyl or as defined below;

R^{11} at each occurrence independently is hydrogen or (C_{1-6})alkyl;

R^{12} and R^{13} independently are (i) (C_{1-6})alkyl optionally substituted with cyano, halo, nitro, $-NR^{14}R^{14}$, $-NR^{14}C(O)OR^{14}$, $-NR^{14}C(O)NR^{14}R^{14}$, $-NR^{14}C(NR^{14})NR^{14}R^{14}$, $-OR^{14}$, $-SR^{14}$, $-C(O)OR^{14}$, $-C(O)NR^{14}R^{14}$, $-S(O)_2NR^{14}R^{14}$, $-P(O)(OR^{14})OR^{14}$, $-OP(O)(OR^{14})OR^{14}$, $-NR^{14}C(O)R^{15}$, $-S(O)R^{15}$, $-S(O)_2R^{15}$, $-C(O)R^{15}$, $-OR^{16}$, $-SR^{16}$, $-S(O)R^{16}$, $-S(O)_2R^{16}$, $-C(O)R^{16}$, $-C(O)OR^{16}$, $-OC(O)R^{16}$, $-NR^{16}R^{17}$, $-NR^{17}C(O)R^{16}$, $-NR^{17}C(O)OR^{16}$, $-C(O)NR^{16}R^{17}$, $-S(O)_2NR^{16}R^{17}$, $-NR^{17}C(O)NR^{16}R^{17}$ or $-NR^{17}C(NR^{17})NR^{16}R^{17}$, wherein R^{14} at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl, R^{15} (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl, R^{16} is (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl, (C_{9-12})polycycloaryl(C_{0-6})alkyl or hetero(C_{8-12})polycycloaryl(C_{0-6})alkyl and R^{17} is hydrogen or (C_{1-6})alkyl, and wherein within R^{16} said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, polycycloaryl or heterpolycycloaryl ring optionally is substituted by a group selected from $-R^{18}$, $-X^5OR^{18}$, $-X^5SR^{18}$, $-X^5S(O)R^{18}$, $-X^5S(O)_2R^{18}$, $-X^5C(O)R^{18}$, $-X^5C(O)OR^{18}$, $-X^5OC(O)R^{18}$, $-X^5NR^{18}R^{19}$, $-X^5NR^{19}C(O)R^{18}$, $-X^5NR^{19}C(O)OR^{18}$, $-X^5C(O)NR^{18}R^{19}$, $-X^5S(O)_2NR^{18}R^{19}$, $-X^5NR^{19}C(O)NR^{18}R^{19}$ or $-X^5NR^{19}C(NR^{19})NR^{18}R^{19}$, wherein X^5 is a bond or (C_{1-6})alkylene, R^{18} is hydrogen or (C_{1-6})alkyl and R^{19} is

(C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl, (C_{9-12})polycycloaryl(C_{0-6})alkyl or hetero(C_{8-12})polycycloaryl(C_{0-6})alkyl, or (ii) a group selected from (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl, (C_{9-12})polycycloaryl(C_{0-6})alkyl and hetero(C_{8-12})polycycloaryl(C_{0-6})alkyl, wherein said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, polycycloaryl or heterpolycycloaryl ring optionally is substituted by a group selected from $-R^{18}$, $-X^5OR^{18}$, $-X^5SR^{18}$, $-X^5S(O)R^{18}$, $-X^5S(O)_2R^{18}$, $-X^5C(O)R^{18}$, $-X^5C(O)OR^{18}$, $-X^5OC(O)R^{18}$, $-X^5NR^{18}R^{19}$, $-X^5NR^{19}C(O)R^{18}$, $-X^5NR^{19}C(O)OR^{18}$, $-X^5C(O)NR^{18}R^{19}$, $-X^5S(O)_2NR^{18}R^{19}$, $-X^5NR^{19}C(O)NR^{18}R^{19}$ or $-X^5NR^{19}C(NR^{19})NR^{18}R^{19}$, wherein X^5, R^{18} and R^{19} are as defined above; wherein within R^{12} and/or R^{13} any alicyclic or aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted (C_{1-4})alkyl, nitro, $-X^5NR^{14}R^{14}$, $-X^5NR^{14}C(O)OR^{14}$, $-X^5NR^{14}C(O)NR^{14}R^{14}$, $-X^5NR^{14}C(NR^{14})NR^{14}R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{14}$, $-X^5S(O)_2NR^{14}R^{14}$, $-X^5P(O)(OR^{14})OR^{14}$, $-X^5OP(O)(OR^{14})OR^{14}$, $-X^5NR^{14}C(O)R^{15}$, $-X^5S(O)R^{15}$, $-X^5S(O)_2R^{15}$ and $-X^5C(O)R^{15}$, wherein X^5, R^{14} and R^{15} are as defined above; or

R^{12} together with R^9 and/or R^{13} together with R^{10} form trimethylene, tetramethylene or phenylene-1,2-dimethylene, , optionally substituted with 1 to 3 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted (C_{1-4})alkyl, nitro, oxo, $-X^5NR^{14}C(O)OR^{14}$, $-X^5NR^{14}C(O)NR^{14}R^{14}$, $-X^5NR^{14}C(NR^{14})NR^{14}R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{14}$, $-X^5S(O)_2NR^{14}R^{14}$, $-X^5P(O)(OR^{14})OR^{14}$, $-X^5OP(O)(OR^{14})OR^{14}$, $-X^5NR^{14}C(O)R^{15}$, $-X^5S(O)R^{15}$, $-X^5S(O)_2R^{15}$ and $-X^5C(O)R^{15}$, wherein X^5, R^{14} and R^{15} are as defined above; and

R^1 is $-X^6X^7R^{20}$, wherein X^6 is -C(O)-, -C(O)C(O)- or $-S(O)_2-$, X^7 is a bond, -O- or $-NR^{21}-$, wherein R^{21} is hydrogen or (C_{1-6})alkyl, and R^{20} is (i) (C_{1-6})alkyl optionally substituted by cyano, halo, nitro, $-NR^{14}R^{14}$, $-NR^{14}C(O)OR^{14}$, $-NR^{14}C(O)NR^{14}R^{14}$, $-NR^{14}C(NR^{14})NR^{14}R^{14}$, $-OR^{14}$, $-SR^{14}$, $-C(O)OR^{14}$, $-C(O)NR^{14}R^{14}$, $-S(O)_2NR^{14}R^{14}$, $-P(O)(OR^{14})OR^{14}$, $-OP(O)(OR^{14})OR^{14}$, $-NR^{14}C(O)R^{15}$, $-S(O)R^{15}$, $-S(O)_2R^{15}$, $-C(O)R^{15}$, $-OR^{22}$, $-SR^{22}$, $-S(O)R^{22}$, $-S(O)_2R^{22}$, $-C(O)R^{22}$, $-C(O)OR^{22}$, $-C(O)NR^{22}R^{23}$, $-NR^{22}R^{23}$, $-NR^{23}C(O)R^{22}$, $-NR^{23}C(O)OR^{22}$,

$-NR^{23}C(O)NR^{22}R^{23}$ or $-NR^{23}C(NR^{23})NR^{22}R^{23}$, wherein R^{14} and R^{15} are as defined above, R^{22} is (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl, (C_{9-12})bicycloaryl(C_{0-6})alkyl or hetero(C_{8-12})bicycloaryl(C_{0-6})alkyl and R^{23} at each occurrence independently is hydrogen or (C_{1-6})alkyl, or

(ii) (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, diphenyl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl, dihetero(C_{5-6})aryl(C_{0-6})alkyl, (C_{9-12})bicycloaryl(C_{0-6})alkyl or hetero(C_{8-12})bicycloaryl(C_{0-6})alkyl wherein said cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be substituted by $-R^{24}$, $-X^5OR^{24}$, $-X^5SR^{24}$, $-X^5S(O)R^{24}$, $-X^5S(O)_2R^{24}$, $-X^5C(O)R^{24}$, $-X^5C(O)OR^{24}$, $-X^5C(O)NR^{24}R^{25}$, $-X^5NR^{24}R^{25}$, $-X^5NR^{25}C(O)R^{24}$, $-X^5NR^{25}C(O)OR^{24}$, $-X^5NR^{25}C(O)NR^{24}R^{25}$ or $-X^5NR^{25}C(NR^{25})NR^{24}R^{25}$, wherein X^5 is as defined above, R^{24} is (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl, (C_{9-12})bicycloaryl(C_{0-6})alkyl or hetero(C_{8-12})bicycloaryl(C_{0-6})alkyl and R^{25} at each occurrence independently is hydrogen or (C_{1-6})alkyl; wherein within R^1 any alicyclic or aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted (C_{1-4})alkyl, nitro, $-X^5NR^{14}R^{14}$, $-X^5NR^{14}C(O)OR^{14}$, $-X^5NR^{14}C(O)NR^{14}R^{14}$, $-X^5NR^{14}C(NR^{14})NR^{14}R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{14}$, $-X^5S(O)_2NR^{14}R^{14}$, $-X^5P(O)(OR^{14})OR^{14}$, $-X^5OP(O)(OR^{14})OR^{14}$, $-X^5NR^{14}C(O)R^{15}$, $-X^5S(O)R^{15}$, $-X^5S(O)_2R^{15}$ and $-X^5C(O)R^{15}$, wherein X^5, R^{14} and R^{15} are as defined above; or when X^2 is a divalent group of formula (a) or (b) then R^1 may also represent hydrogen, carboxy, oxalo or carbamoyl;

R^2 is hydrogen or (C_{1-6})alkyl;

R^3 is (i) (C_{1-6})alkyl optionally substituted with cyano, halo, nitro, $-SR^{24}$, $-C(O)OR^{24}$, $-C(O)NR^{24}R^{24}$, $-P(O)(OR^{24})OR^{24}$, $-OP(O)(OR^{24})OR^{24}$, $-S(O)R^{25}$, $-S(O)_2R^{25}$ or $-C(O)R^{25}$, wherein R^{24} at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl and R^{25} (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl, or (ii) (C_{5-6})cycloalkyl(C_{2-3})alkyl, hetero(C_{3-6})cycloalkyl(C_{2-3})alkyl, (C_{6-12})aryl(C_{2-3})alkyl or hetero(C_{5-6})aryl(C_{2-3})alkyl, wherein said cycloalkyl, heterocycloalkyl, aryl or heteroaryl optionally is substituted further with 1 to 5 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted (C_{1-4})alkyl, nitro, $-X^5NR^{14}C(O)OR^{14}$, $-X^5NR^{14}C(O)NR^{14}R^{14}$, $-X^5NR^{14}C(NR^{14})NR^{14}R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{14}$, $-X^5S(O)_2NR^{14}R^{14}$, $-X^5P(O)(OR^{14})OR^{14}$, $-X^5OP(O)(OR^{14})OR^{14}$, $-X^5NR^{14}C(O)R^{15}$, $-X^5S(O)R^{15}$, $-X^5S(O)_2R^{15}$ and $-X^5C(O)R^{15}$, wherein

X^5, R^{14} and R^{15} are as defined above, provided that when R^3 is unsubstituted (C_{1-5})alkyl and R^4 is hydrogen or unsubstituted (C_{1-5})alkyl, then X^2 may not represent (i) a bond when R^1 is $-C(O)R^{20}$, $-C(O)_2R^{20}$ or $-S(O)_2R^{20}$ in which R^{20} is (C_{1-6})alkyl, phenyl(C_{1-4})alkyl, phenyl, (C_{3-7})cycloalkyl, camphan-10-yl, naphth-1-yl, naphth-2-yl, phenyl substituted by one or more of (C_{1-4})alkyl, perfluoro(C_{1-4})alkyl, (C_{1-4})alkoxy, hydroxy, halo, amido, nitro, amino, (C_{1-4})alkylamino, (C_{1-4})dialkylamino, carboxy or (C_{1-4})alkoxycarbonyl, or naphth-1-yl or naphth-2-yl substituted by one or more of (C_{1-4})alkyl, perfluoro(C_{1-4})alkyl, (C_{1-4})alkoxy, hydroxy, halo, amido, nitro, amino, carboxy or (C_{1-4})alkoxycarbonyl or (ii) a divalent group of formula (a) or (b) in which the moiety R^{12} is methyl, isopropyl, *n*-butyl, *sec*-butyl, *tert*-butyl, 1-methylpropyl, benzyl, naphth-1-ylmethyl, naphth-2-ylmethyl, thien-2-ylmethyl, thien-3-ylmethyl, or wherein R^9 and R^{12} form ethylene, trimethylene, hydroxy-substituted trimethylene, tetramethylene or phenylene-1,2-dimethylene; or

R^3 and R^4 taken together with the carbon atom to which both R^3 and R^4 are attached form (C_{3-8})cycloalkylene or (C_{3-8})heterocycloalkylene, wherein said cycloalkylene or heterocycloalkylene is optionally substituted with 1 to 3 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted (C_{1-4})alkyl, nitro, $-X^5NR^{14}C(O)OR^{14}$, $-X^5NR^{14}C(O)NR^{14}R^{14}$, $-X^5NR^{14}C(NR^{14})NR^{14}R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{14}$, $-X^5S(O)_2NR^{14}R^{14}$, $-X^5P(O)(OR^{14})OR^{14}$, $-X^5OP(O)(OR^{14})OR^{14}$, $-X^5NR^{14}C(O)R^{15}$, $-X^5S(O)R^{15}$, $-X^5S(O)_2R^{15}$ and $-X^5C(O)R^{15}$, wherein X^5, R^{14} and R^{15} are as defined above;

R^3 and R^4 taken together with the carbon atom to which both R^3 and R^4 are attached form (C_{3-8})cycloalkylene or (C_{3-8})heterocycloalkylene, wherein said cycloalkylene or heterocycloalkylene is optionally substituted with 1 to 3 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted (C_{1-4})alkyl, nitro, $-X^5NR^{14}C(O)OR^{14}$, $-X^5NR^{14}C(O)NR^{14}R^{14}$, $-X^5NR^{14}C(NR^{14})NR^{14}R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{14}$, $-X^5S(O)_2NR^{14}R^{14}$, $-X^5P(O)(OR^{14})OR^{14}$, $-X^5OP(O)(OR^{14})OR^{14}$, $-X^5NR^{14}C(O)R^{15}$, $-X^5S(O)R^{15}$, $-X^5S(O)_2R^{15}$ and $-X^5C(O)R^{15}$, wherein X^5, R^{14} and R^{15} are as defined above;

R^4 is hydrogen, (C_{1-6})alkyl or as defined above;

R^5 is hydrogen and R^6 is hydroxy or R^5 and R^6 together form oxo;

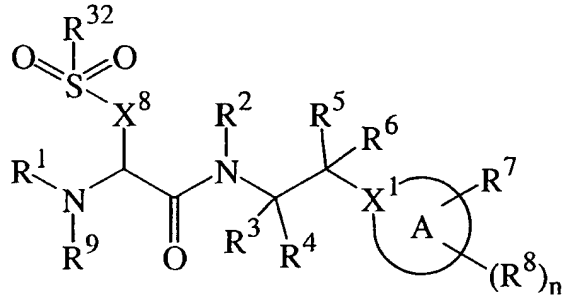
R^7 is a group selected from cyano, halo, nitro, $-R^{29}$, $-X^5NR^{29}R^{30}$, $-X^5NR^{30}C(O)OR^{29}$, $-X^5NR^{30}C(O)NR^{29}R^{30}$, $-X^5NR^{30}C(NR^{30})NR^{29}R^{30}$, $-X^5OR^{29}$, $-X^5SR^{29}$, $-X^5C(O)OR^{29}$, $-X^5C(O)NR^{29}R^{30}$, $-X^5S(O)_2NR^{29}R^{30}$, $-X^5P(O)(OR^{30})OR^{29}$, $-X^5OP(O)(OR^{29})OR^{29}$,

$-X^5NR^{30}C(O)R^{20}$, $-X^5S(O)R^{20}$, $-X^5S(O)_2R^{20}$, $-X^5C(O)R^{20}$ and $-C(O)NR^{42}CHR^{43}C(O)OR^{29}$, wherein X^5 and R^{20} are as defined as above, R^{29} is hydrogen or $-R^{20}$, wherein R^{20} is defined as above, R^{30} at each occurrence is hydrogen or (C_{1-6})alkyl, R^{42} is hydrogen, (C_{1-6})alkyl or together with R^{43} forms trimethylene, tetramethylene or phenylene-1,2-dimethylene, optionally substituted with hydroxy or oxo, and R^{43} is as defined above or is (i) (C_{1-6})alkyl optionally substituted with cyano, halo, nitro, $-NR^{14}R^{14}$, $-NR^{14}C(O)OR^{14}$, $-NR^{14}C(O)NR^{14}R^{14}$, $-NR^{14}C(NR^{14})NR^{14}R^{14}$, $-OR^{14}$, $-SR^{14}$, $-C(O)OR^{14}$, $-C(O)NR^{14}R^{14}$, $-S(O)_2NR^{14}R^{14}$, $-P(O)(OR^{14})OR^{14}$, $-OP(O)(OR^{14})OR^{14}$, $-NR^{14}C(O)R^{15}$, $-S(O)R^{15}$, $-S(O)_2R^{15}$, $-C(O)R^{15}$, $-OR^{16}$, $-SR^{16}$, $-S(O)R^{16}$, $-S(O)_2R^{16}$, $-C(O)R^{16}$, $-C(O)OR^{16}$, $-OC(O)R^{16}$, $-NR^{16}R^{17}$, $-NR^{17}C(O)R^{16}$, $-NR^{17}C(O)OR^{16}$, $-C(O)NR^{16}R^{17}$, $-S(O)_2NR^{16}R^{17}$, $-NR^{17}C(O)NR^{16}R^{17}$ or $-NR^{17}C(NR^{17})NR^{16}R^{17}$ or (ii) a group selected from (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl, (C_{9-12})polycycloaryl(C_{0-6})alkyl and hetero(C_{8-12})polycycloaryl(C_{0-6})alkyl, wherein said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, polycycloaryl or heterpolycycloaryl ring optionally is substituted by a group selected from $-R^{18}$, $-X^5OR^{18}$, $-X^5SR^{18}$, $-X^5S(O)R^{18}$, $-X^5S(O)_2R^{18}$, $-X^5C(O)R^{18}$, $-X^5C(O)OR^{18}$, $-X^5OC(O)R^{18}$, $-X^5NR^{18}R^{19}$, $-X^5NR^{19}C(O)R^{18}$, $-X^5NR^{19}C(O)OR^{18}$, $-X^5C(O)NR^{18}R^{19}$, $-X^5S(O)_2NR^{18}R^{19}$, $-X^5NR^{19}C(O)NR^{18}R^{19}$ or $-X^5NR^{19}C(NR^{19})NR^{18}R^{19}$, wherein X^5, R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} are as defined above; wherein within R^7 any alicyclic or aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted (C_{1-4})alkyl, nitro, $-X^5NR^{14}R^{14}$, $-X^5NR^{14}C(O)OR^{14}$, $-X^5NR^{14}C(O)NR^{14}R^{14}$, $-X^5NR^{14}C(NR^{14})NR^{14}R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{14}$, $-X^5S(O)_2NR^{14}R^{14}$, $-X^5P(O)(OR^{14})OR^{14}$, $-X^5OP(O)(OR^{14})OR^{14}$, $-X^5NR^{14}C(O)R^{15}$, $-X^5S(O)R^{15}$, $-X^5S(O)_2R^{15}$ and $-X^5C(O)R^{15}$, wherein X^5, R^{14} and R^{15} are as defined above; and

R^8 at each occurrence independently is selected from (C_{1-6})alkyl, halo-substituted (C_{1-4})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted (C_{1-4})alkyl, nitro, $-X^5NR^{14}R^{14}$, $-X^5NR^{14}C(O)OR^{14}$, $-X^5NR^{14}C(O)NR^{14}R^{14}$, $-X^5NR^{14}C(NR^{14})NR^{14}R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{14}$, $-X^5S(O)_2NR^{14}R^{14}$, $-X^5P(O)(OR^{14})OR^{14}$, $-X^5OP(O)(OR^{14})OR^{14}$, $-X^5NR^{14}C(O)R^{15}$, $-X^5S(O)R^{15}$, $-X^5S(O)_2R^{15}$ and $-X^5C(O)R^{15}$, wherein X^5 is a bond or (C_{1-6})alkylene, R^{14} at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl and R^{15} (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of

isomers; and the pharmaceutically acceptable salts thereof.

In another particular embodiment, the present invention relates to a compound of Formula II:



II

in which:

A comprises a heteromonocyclic ring containing 5 to 6 ring member atoms or a fused heteropolycyclic ring system containing 8 to 14 ring member atoms, wherein each ring contains 5 to 7 ring member atoms, X^1 is a ring member carbon atom and each ring member atom other than X^1 is a carbon atom or a heteroatom, with the proviso that at least one ring member atom is a heteroatom;

n is 0, 1, 2 or 3;

X^1 is =C- or -CH-;

X^8 is (C_{1-2})alkylene;

R^1 is hydrogen, carboxy, oxalo, carbamoyl or $-X^6X^7R^{20}$, wherein X^6 is -C(O)-, -C(O)C(O)- or $-S(O)_2-$, X^7 is a bond, -O- or $-NR^{21}-$, wherein R^{21} is hydrogen or (C_{1-6})alkyl, and R^{20} is (i) (C_{1-6})alkyl optionally substituted by cyano, halo, nitro, $-NR^{14}R^{14}$, $-NR^{14}C(O)OR^{14}$, $-NR^{14}C(O)NR^{14}R^{14}$, $-NR^{14}C(NR^{14})NR^{14}R^{14}$, $-OR^{14}$, $-SR^{14}$, $-C(O)OR^{14}$, $-C(O)NR^{14}R^{14}$, $-S(O)_2NR^{14}R^{14}$, $-P(O)(OR^{14})OR^{14}$, $-OP(O)(OR^{14})OR^{14}$, $-NR^{14}C(O)R^{15}$, $-S(O)R^{15}$, $-S(O)_2R^{15}$, $-C(O)R^{15}$, $-OR^{22}$, $-SR^{22}$, $-S(O)R^{22}$, $-S(O)_2R^{22}$, $-C(O)R^{22}$, $-C(O)OR^{22}$, $-C(O)NR^{22}R^{23}$, $-NR^{22}R^{23}$, $-NR^{23}C(O)R^{22}$, $-NR^{23}C(O)OR^{22}$,$-NR^{23}C(O)NR^{22}R^{23}$ or $-NR^{23}C(NR^{23})NR^{22}R^{23}$, wherein R^{14} at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl, R^{15} is (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl, R^{22} is (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl, (C_{9-12})bicycloaryl(C_{0-6})alkyl or hetero(C_{8-12})bicycloaryl(C_{0-6})alkyl and R^{23} at each occurrence independently is hydrogen or (C_{1-6})alkyl, or (ii) (C_{3-12})cycloalkyl(C_{0-6})alkyl,

hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl, (C_{9-12})bicycloaryl(C_{0-6})alkyl or hetero(C_{8-12})bicycloaryl(C_{0-6})alkyl or

(iii) (C_{3-6})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-6})cycloalkyl(C_{0-6})alkyl, phenyl(C_{0-6})alkyl or hetero(C_{5-6})aryl(C_{0-6})alkyl substituted by $-X^5OR^{24}$, $-X^5SR^{24}$, $-X^5S(O)R^{24}$, $-X^5S(O)_2R^{24}$, $-X^5C(O)R^{24}$, $-X^5C(O)OR^{24}$, $-X^5C(O)NR^{24}R^{25}$, $-X^5NR^{24}R^{25}$, $-X^5NR^{25}C(O)R^{24}$, $-X^5NR^{25}C(O)OR^{24}$, $-X^5NR^{25}C(O)NR^{24}R^{25}$ or $-X^5NR^{25}C(NR^{25})NR^{24}R^{25}$, wherein X^5 is a bond or (C_{1-6})alkylene, R^{24} is (C_{3-6})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-6})cycloalkyl(C_{0-6})alkyl, phenyl(C_{0-6})alkyl or hetero(C_{5-6})aryl(C_{0-6})alkyl and R^{25} at each occurrence independently is hydrogen or (C_{1-6})alkyl; wherein within R^1 any alicyclic or aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted (C_{1-4})alkyl, nitro, $-X^5NR^{14}R^{14}$, $-X^5NR^{14}C(O)OR^{14}$, $-X^5NR^{14}C(O)NR^{14}R^{14}$, $-X^5NR^{14}C(NR^{14})NR^{14}R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{14}$, $-X^5S(O)_2NR^{14}R^{14}$, $-X^5P(O)(OR^{14})OR^{14}$, $-X^5OP(O)(OR^{14})OR^{14}$, $-X^5NR^{14}C(O)R^{15}$, $-X^5S(O)R^{15}$, $-X^5S(O)_2R^{15}$ and $-X^5C(O)R^{15}$, wherein X^5, R^{14} and R^{15} are as defined above;

R^2 is hydrogen or (C_{1-6})alkyl;

R^3 is (i) (C_{1-6})alkyl optionally substituted with cyano, halo, nitro, $-NR^{14}R^{14}$, $-NR^{14}C(O)OR^{14}$, $-NR^{14}C(O)NR^{14}R^{14}$, $-NR^{14}C(NR^{14})NR^{14}R^{14}$, $-OR^{14}$, $-SR^{14}$, $-C(O)OR^{14}$, $-C(O)NR^{14}R^{14}$, $-S(O)_2NR^{14}R^{14}$, $-P(O)(OR^{14})OR^{14}$, $-OP(O)(OR^{14})OR^{14}$, $-NR^{14}C(O)R^{15}$, $-S(O)R^{15}$, $-S(O)_2R^{15}$, $-C(O)R^{15}$, $-OR^{16}$, $-SR^{16}$, $-S(O)R^{16}$, $-S(O)_2R^{16}$, $-C(O)R^{16}$, $-C(O)OR^{16}$, $-OC(O)R^{16}$, $-NR^{16}R^{17}$, $-NR^{17}C(O)R^{16}$, $-NR^{17}C(O)OR^{16}$, $-C(O)NR^{16}R^{17}$, $-S(O)_2NR^{16}R^{17}$, $-NR^{17}C(O)NR^{16}R^{17}$ or $-NR^{17}C(NR^{17})NR^{16}R^{17}$, wherein R^{14} at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl, R^{15} is (C_{1-6})alkyl or halo-substituted (C_{1-3})alkyl, R^{16} is (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl, (C_{9-12})polycycloaryl(C_{0-6})alkyl or hetero(C_{8-12})polycycloaryl(C_{0-6})alkyl and R^{17} is hydrogen or (C_{1-6})alkyl, and wherein within R^{16} said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, polycycloaryl or heterpolycycloaryl ring optionally is substituted by a group selected from $-R^{18}$, $-X^5OR^{18}$, $-X^5SR^{18}$, $-X^5S(O)R^{18}$, $-X^5S(O)_2R^{18}$, $-X^5C(O)R^{18}$, $-X^5C(O)OR^{18}$, $-X^5OC(O)R^{18}$, $-X^5NR^{18}R^{19}$, $-X^5NR^{19}C(O)R^{18}$, $-X^5NR^{19}C(O)OR^{18}$, $-X^5C(O)NR^{18}R^{19}$, $-X^5S(O)_2NR^{18}R^{19}$, $-X^5NR^{19}C(O)NR^{18}R^{19}$ or $-X^5NR^{19}C(NR^{19})NR^{18}R^{19}$, wherein X^5 is as defined above, R^{18} is hydrogen or (C_{1-6})alkyl and R^{19} is (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl,

hetero(C_{5-12})aryl(C_{0-6})alkyl, (C_{9-12})polycycloaryl(C_{0-6})alkyl or hetero(C_{8-12})polycycloaryl(C_{0-6})alkyl, or (ii) a group selected from (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl, (C_{9-12})polycycloaryl(C_{0-6})alkyl and hetero(C_{8-12})polycycloaryl(C_{0-6})alkyl, wherein said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, polycycloaryl or heterpolycycloaryl ring optionally is substituted by a group selected from $-R^{18}$, $-X^5OR^{18}$, $-X^5SR^{18}$, $-X^5S(O)R^{18}$, $-X^5S(O)_2R^{18}$, $-X^5C(O)R^{18}$, $-X^5C(O)OR^{18}$, $-X^5OC(O)R^{18}$, $-X^5NR^{18}R^{19}$, $-X^5NR^{19}C(O)R^{18}$, $-X^5NR^{19}C(O)OR^{18}$, $-X^5C(O)NR^{18}R^{19}$, $-X^5S(O)_2NR^{18}R^{19}$, $-X^5NR^{19}C(O)NR^{18}R^{19}$ or $-X^5NR^{19}C(NR^{19})NR^{18}R^{19}$, wherein X^5, R^{18} and R^{19} are as defined above; wherein within R^{12} and/or R^{13} any alicyclic or aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted (C_{1-4})alkyl, nitro, $-X^5NR^{14}R^{14}$, $-X^5NR^{14}C(O)OR^{14}$, $-X^5NR^{14}C(O)NR^{14}R^{14}$, $-X^5NR^{14}C(NR^{14})NR^{14}R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{14}$, $-X^5S(O)_2NR^{14}R^{14}$, $-X^5P(O)(OR^{14})OR^{14}$, $-X^5OP(O)(OR^{14})OR^{14}$, $-X^5NR^{14}C(O)R^{15}$, $-X^5S(O)R^{15}$, $-X^5S(O)_2R^{15}$ and $-X^5C(O)R^{15}$, wherein X^5, R^{14} and R^{15} are as defined above, or

R^3 and R^4 taken together with the carbon atom to which both R^3 and R^4 are attached form (C_{3-8})cycloalkylene or (C_{3-8})heterocycloalkylene, wherein said cycloalkylene or heterocycloalkylene is optionally substituted with 1 to 3 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted (C_{1-4})alkyl, nitro, $-X^5NR^{14}C(O)OR^{14}$, $-X^5NR^{14}C(O)NR^{14}R^{14}$, $-X^5NR^{14}C(NR^{14})NR^{14}R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{14}$, $-X^5S(O)_2NR^{14}R^{14}$, $-X^5P(O)(OR^{14})OR^{14}$, $-X^5OP(O)(OR^{14})OR^{14}$, $-X^5NR^{14}C(O)R^{15}$, $-X^5S(O)R^{15}$, $-X^5S(O)_2R^{15}$ and $-X^5C(O)R^{15}$, wherein X^5, R^{14} and R^{15} are as defined above;

R^4 is hydrogen, (C_{1-6})alkyl or as defined above;

R^5 is hydrogen and R^6 is hydroxy or R^5 and R^6 together form oxo;

R^7 is a group selected from cyano, halo, nitro, $-R^{29}$, $-X^5NR^{29}R^{30}$, $-X^5NR^{30}C(O)OR^{29}$, $-X^5NR^{30}C(O)NR^{29}R^{30}$, $-X^5NR^{30}C(NR^{30})NR^{29}R^{30}$, $-X^5OR^{29}$, $-X^5SR^{29}$, $-X^5C(O)OR^{29}$, $-X^5C(O)NR^{29}R^{30}$, $-X^5S(O)_2NR^{29}R^{30}$, $-X^5P(O)(OR^{30})OR^{29}$, $-X^5OP(O)(OR^{29})OR^{29}$, $-X^5NR^{30}C(O)R^{31}$, $-X^5S(O)R^{31}$, $-X^5S(O)_2R^{31}$ and $-X^5C(O)R^{31}$, wherein X^5 is as defined above, R^{29} is hydrogen or $-R^{31}$, R^{30} at each occurrence is hydrogen or (C_{1-6})alkyl and R^{31} is (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl or hetero(C_{5-12})aryl(C_{0-6})alkyl, wherein within R^7 any alicyclic or aromatic ring system present may

be substituted further by 1 to 5 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted (C_{1-4})alkyl, nitro, $-X^5NR^{14}R^{14}$, $-X^5NR^{14}C(O)OR^{14}$, $-X^5NR^{14}C(O)NR^{14}R^{14}$, $-X^5NR^{14}C(NR^{14})NR^{14}R^{14}$; $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{14}$, $-X^5S(O)_2NR^{14}R^{14}$, $-X^5P(O)(OR^{14})OR^{14}$, $-X^5OP(O)(OR^{14})OR^{14}$, $-X^5NR^{14}C(O)R^{15}$, $-X^5S(O)R^{15}$, $-X^5S(O)_2R^{15}$ and $-X^5C(O)R^{15}$, wherein X^5, R^{14} and R^{15} are as defined above; and

R^8 at each occurrence independently is selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted (C_{1-4})alkyl, nitro, $-X^5NR^{14}R^{14}$, $-X^5NR^{14}C(O)OR^{14}$, $-X^5NR^{14}C(O)NR^{14}R^{14}$, $-X^5NR^{14}C(NR^{14})NR^{14}R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{14}$, $-X^5S(O)_2NR^{14}R^{14}$, $-X^5P(O)(OR^{14})OR^{14}$, $-X^5OP(O)(OR^{14})OR^{14}$, $-X^5NR^{14}C(O)R^{15}$, $-X^5S(O)R^{15}$, $-X^5S(O)_2R^{15}$ and $-X^5C(O)R^{15}$, wherein X^5, R^{14} and R^{15} are as defined above;

R^9 is hydrogen or (C_{1-6})alkyl; and

R^{32} is (C_{1-8})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl, (C_{9-12})polycycloaryl(C_{0-6})alkyl or hetero(C_{8-12})polycycloaryl(C_{0-6})alkyl, wherein within R^{30} any alicyclic or aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted (C_{1-4})alkyl, nitro, $-X^5NR^{14}R^{14}$, $-X^5NR^{14}C(O)OR^{14}$, $-X^5NR^{14}C(O)NR^{14}R^{14}$, $-X^5NR^{14}C(NR^{14})NR^{14}R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{14}$, $-X^5S(O)_2NR^{14}R^{14}$, $-X^5P(O)(OR^{14})OR^{14}$, $-X^5OP(O)(OR^{14})OR^{14}$, $-X^5NR^{14}C(O)R^{15}$, $-X^5S(O)R^{15}$, $-X^5S(O)_2R^{15}$ and $-X^5C(O)R^{15}$, wherein X^5, R^{14} and R^{15} are as defined above; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.

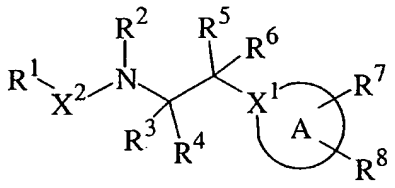
In another particular embodiment, the present invention relates to a pharmaceutical composition which contains a compound of Formula I or II, or a *N*-oxide derivative, prodrug derivative, individual isomer or mixture of isomers, or a pharmaceutically acceptable salt thereof in admixture with one or more suitable excipients.

In another particular embodiment, the present invention relates to method of treating a disease in an animal in which inhibition of a cysteine protease can prevent, inhibit or ameliorate the pathology and/or symptomatology of the disease, which method comprises administering to the animal a therapeutically effective amount of compound of Formula I or II or a *N*-oxide derivative, prodrug derivative, individual isomer or mixture of isomers or a pharmaceutically

acceptable salt thereof.

In another particular embodiment, the present invention relates to processes for preparing compounds of Formula I and II and the *N*-oxide derivatives, prodrug derivative, protected derivatives, individual isomers and mixtures of isomers, and the pharmaceutically acceptable salts thereof as set forth in "Detailed Description of the Invention".

In another particular embodiment, the present invention relates to protease inhibitors of Formula III:



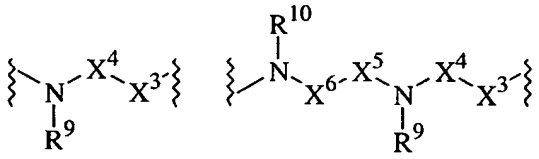
III

in which:

A comprises a heteromonocyclic radical containing 5 to 6 annular atoms or a fused heteropolycyclic radical containing 8 to 14 annular atoms, wherein each ring contains 5 to 7 annular atoms, X^1 is an annular carbon atom and each annular atom other than X^1 optionally is a heteroatom, with the proviso that when A is a heteromonocyclic radical containing 5 annular atoms, no more than two of the annular atoms comprising the ring are heteroatoms;

X^1 is selected from =C- and -CH-;

X^2 is a bond or a divalent group of Formula (a) or (b):



(a) (b)

wherein:

X^3 and X^5 independently are -C(O)- or $-S(O)_2-$,

X^4 is $-CHR^{11}-$, $-CH_2CHR^{11}-$ or $-CHR^{11}CH_2-$ and X^6 is $-CHR^{12}-$, $-CH_2CHR^{12}-$ or $-CHR^{12}CH_2-$ wherein:

R^{11} and R^{12} are independently (i) (C_{1-6})alkyl or halo-substituted(C_{1-6})alkyl optionally substituted with $-OR^{13}$, $-SR^{13}$, $-S(O)R^{13}$,

$-S(O)_2R^{13}$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-NR^{13}R^{14}$, $-NR^{14}C(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-S(O)_2NR^{13}R^{14}$, $-NR^{14}C(O)NR^{13}R^{14}$ or $-NR^{14}C(NR^{14})NR^{13}R^{14}$, wherein R^{13} is hydrogen, (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{0-3})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-3})alkyl, (C_{6-12})aryl(C_{0-3})alkyl or hetero(C_{5-12})aryl(C_{0-3})alkyl and R^{14} is hydrogen or (C_{1-6})alkyl, or

(ii) (C_{3-12})cycloalkyl(C_{0-3})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-3})alkyl, (C_{6-12})aryl(C_{0-3})alkyl, hetero(C_{5-12})aryl(C_{0-3})alkyl, (C_{9-12})polycycloaryl(C_{0-3})alkyl or hetero(C_{8-12})polycycloaryl(C_{0-3})alkyl optionally substituted with $-R^{15}$, $-X^7OR^{15}$, $-X^7SR^{15}$, $-S(O)R^{15}$, $-S(O)_2R^{15}$, $-C(O)R^{15}$, $-C(O)OR^{15}$, $-X^7NR^{15}R^{16}$, $-X^7NR^{16}C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-S(O)_2NR^{15}R^{16}$, $-NR^{16}C(O)NR^{15}R^{16}$ or $-NR^{16}C(NR^{16})NR^{15}R^{16}$, wherein X^7 is a bond or methylene, R^{15} is (C_{3-12})cycloalkyl(C_{0-3})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-3})alkyl, (C_{6-12})aryl(C_{0-3})alkyl, hetero(C_{5-12})aryl(C_{0-3})alkyl, (C_{9-12})polycycloaryl(C_{0-3})alkyl or hetero(C_{8-12})polycycloaryl(C_{0-3})alkyl and R^{16} is hydrogen or (C_{1-6})alkyl, or

(iii) together with R^9 or R^{10}, respectively, when X^4 is $-CHR^{11}-$ and/or X^6 is $-CHR^{12}-$, forms trimethylene, tetramethylene or phenylene-1,2-dimethylene, optionally substituted with hydroxy or oxo; wherein any 1 to 3 annular atoms of any aromatic ring with available valences comprising R^{11} and/or R^{12} are optionally independently substituted with halo, nitro, cyano, (C_{1-6})alkyl, halo-substituted(C_{1-6})alkyl, $-OR^{17}$, $-C(O)R^{17}$, $-C(O)OR^{17}$, $-C(O)NR^{17}R^{17}$, $-S(O)_2NR^{17}R^{17}$, $-X^7NR^{17}R^{17}$, $-X^7NR^{17}C(O)OR^{17}$, $-X^7NR^{17}C(O)NR^{17}R^{17}$ or $-X^7NR^{17}C(NR^{17})NR^{17}R^{17}$, wherein X^7 is as defined above and each R^{17} independently is hydrogen or (C_{1-6})alkyl; and

R^9 and R^{10} are independently hydrogen, (C_{1-6})alkyl or as defined above;

R^1 is hydrogen or $-X^8X^9R^{18}$, wherein X^8 is $-C(O)-$ or $-S(O)_2-$, X^9 is a bond, $-O-$ or $-NR^{19}-$, wherein R^{19} is hydrogen or (C_{1-6})alkyl, and R^{18} is (i) (C_{1-6})alkyl or halo-substituted(C_{1-6})alkyl optionally substituted with $-OR^{13}$, $-SR^{13}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-NR^{13}R^{14}$, $-NR^{14}C(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-S(O)_2NR^{13}R^{14}$, $-NR^{14}C(O)NR^{13}R^{14}$ or $-NR^{14}C(NR^{14})NR^{13}R^{14}$, wherein R^{13} and R^{14} are as defined above, or

(ii) (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, diphenyl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl, dihetero(C_{5-6})aryl(C_{0-6})alkyl, (C_{9-12})polycycloaryl(C_{0-6})alkyl or hetero(C_{8-12})polycycloaryl(C_{0-6})alkyl optionally substituted with

$-R^{15}$, $-X^7OR^{15}$, $-X^7SR^{15}$, $-S(O)R^{15}$, $-S(O)_2R^{15}$, $-C(O)R^{15}$, $-C(O)OR^{15}$, $-X^7NR^{15}R^{16}$, $-X^7NR^{16}C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-S(O)_2NR^{15}R^{16}$, $-NR^{16}C(O)NR^{15}R^{16}$ or $-NR^{16}C(NR^{16})NR^{15}R^{16}$, wherein X^7, R^{15} and R^{16} are as defined above; wherein any 1 to 3 annular atoms of any aromatic ring with available valences comprising R^1 optionally independently are substituted with halo, nitro, cyano, (C_{1-6})alkyl, halo-substituted(C_{1-6})alkyl, $-OR^{17}$, $-C(O)R^{17}$, $-C(O)OR^{17}$, $-C(O)NR^{17}R^{17}$, $-S(O)_2NR^{17}R^{17}$, $-X^7NR^{17}R^{17}$, $-X^7NR^{17}C(O)OR^{17}$, $-X^7NR^{17}C(O)NR^{17}R^{17}$ or $-X^7NR^{17}C(NR^{17})NR^{17}R^{17}$, wherein X^7 and R^{17} are as defined above;

R^2 is hydrogen or (C_{1-6})alkyl;

R^3 is phenyl(C_{2-3})alkyl, hetero(C_{5-6})aryl(C_{2-3})alkyl, (C_{5-6})cycloalkyl(C_{2-3})alkyl or hetero(C_{5-6})cycloalkyl(C_{2-3})alkyl, wherein any 1 to 3 annular atoms of any aromatic ring with available valences comprising R^3 optionally independently are substituted with halo, nitro, cyano, (C_{1-6})alkyl, halo-substituted(C_{1-6})alkyl, $-OR^{17}$, $-C(O)R^{17}$, $-C(O)OR^{17}$, $-C(O)NR^{17}R^{17}$, $-S(O)_2NR^{17}R^{17}$, $-X^7NR^{17}R^{17}$, $-X^7NR^{17}C(O)OR^{17}$, $-X^7NR^{17}C(O)NR^{17}R^{17}$ or $-X^7NR^{17}C(NR^{17})NR^{17}R^{17}$, wherein X^7 and R^{17} are as defined above, and R^4 is hydrogen or R^3 and R^4 are both methyl, ethyl or propyl or together with the carbon atom to which both R^3 and R^4 are attached form cyclopropylene, cyclobutylene or cyclopentylene;

R^5 is hydrogen and R^6 is hydroxy or R^5 and R^6 together form oxo;

R^7 is halo, nitro, $-R^{20}$, $-OR^{20}$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-S(O)_2NR^{20}R^{21}$, $-C(O)NR^{20}R^{21}$ or $-C(O)NR^{22}CHR^{23}C(O)OR^{20}$ and bonded to any annular carbon atom with a free valence comprising A, wherein:

R^{20} is hydrogen or R^{18}, wherein R^{18} is as defined above;

R^{21} is hydrogen or (C_{1-6})alkyl;

R^{22} is hydrogen, (C_{1-6})alkyl or together with R^{23} forms trimethylene or phenylene-1,2-dimethylene, optionally substituted with hydroxy or oxo; and

R^{23} is as defined above or is (i) (C_{1-6})alkyl or halo-substituted(C_{1-6})alkyl optionally substituted with $-OR^{13}$, $-SR^{13}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-NR^{13}R^{14}$, $-NR^{14}C(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-S(O)_2NR^{13}R^{14}$, $-NR^{14}C(O)NR^{13}R^{14}$ or $-NR^{14}C(NR^{14})NR^{13}R^{14}$, wherein R^{13} and R^{14} are as defined above, or (ii) (C_{3-10})cycloalkyl(C_{0-3})alkyl, hetero(C_{3-10})cycloalkyl(C_{0-3})alkyl, (C_{6-12})aryl(C_{0-3})alkyl, hetero(C_{5-12})aryl(C_{0-3})alkyl, (C_{9-12})polycycloaryl(C_{0-3})alkyl or hetero(C_{8-12})polycycloaryl(C_{0-3})alkyl optionally substituted with $-R^{15}$, $-X^7OR^{15}$, $-X^7SR^{15}$,

$-S(O)R^{15}$, $-S(O)_2R^{15}$, $-C(O)R^{15}$, $-C(O)OR^{15}$, $-X^7NR^{15}R^{16}$, $-X^7NR^{16}C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-S(O)_2NR^{15}R^{16}$, $-NR^{16}C(O)NR^{15}R^{16}$ or $-NR^{16}C(NR^{16})NR^{15}R^{16}$, wherein X^7, R^{15} and R^{16} are as defined above; wherein any 1 to 3 annular atoms of any aromatic ring with available valences comprising R^{20} and/or R^{21} optionally independently are substituted with halo, nitro, cyano, (C_{1-6})alkyl, halo-substituted(C_{1-6})alkyl, $-OR^{17}$, $-C(O)R^{17}$, $-C(O)OR^{17}$, $-C(O)NR^{17}R^{17}$, $-S(O)_2NR^{17}R^{17}$, $-X^7NR^{17}R^{17}$, $-X^7NR^{17}C(O)OR^{17}$, $-X^7NR^{17}C(O)NR^{17}R^{17}$ or $-X^7NR^{17}C(NR^{17})NR^{17}R^{17}$, wherein X^7 and R^{17} are as defined above; and

R^8 is hydrogen, halo, hydroxy, formyl, carboxy, carbamoyl, sulfamoyl or (C_{1-6})alkyl and bonded to any annular carbon atom with a free valence comprising A; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

Definitions:

Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the meanings given this Section:

"Alicyclic" means a moiety characterized by arrangement of the carbon atoms in closed non-aromatic ring structures having properties resembling those of aliphatics and may be saturated or partially unsaturated with two or more double or triple bonds.

"Aliphatic" means a moiety characterized by straight or branched chain arrangement of the constituent carbon atoms and may be saturated or partially unsaturated with two or more double or triple bonds.

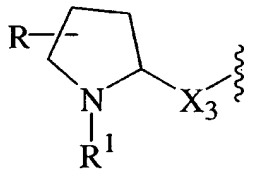
"Alkenyl" means alkyl, as defined in this Application, provided that the radical is comprised of at least one double bond. Hence, optionally substituted (C_{2-6})alkenyl as used in this Application to define R^{32} includes 2-bromovinyl (-CH=CHBr), buta-1,3-dienyl (-CH=CH-CH=CH_2), 2-chloro-1-methylpropenyl (-C(CH_3)=CCl-CH_3), 2-chlorovinyl (-CH=CHCl), 4-isopropenyl (-C(CH_3)=CH_2), 1-methylpropenyl (-C(CH_3)=CH-CH_3), 2-methylpropenyl (-CH=C(CH_3)$_2$), 2-nitrovinyl (-CH=CHNO_2), propenyl (-CH=CH-CH_3),

2-trifluoromethylvinyl (-CH=CH-CF_3), trifluorovinyl (-CF=CF_2), vinyl (-CH=CH_2), and the like).

"Alkoxy" means the radical -OR, wherein R is alkyl as defined in this Application, having the number of carbon atoms indicated (e.g., (C_{1-4})alkoxy includes the radicals methoxy, ethoxy, propoxy, isopropoxy, butoxy, *sec*-butoxy, isobutoxy, *tert*-butoxy, vinyloxy, allyloxy, 1-propenyloxy, isopropenyloxy, 1-butenyloxy, 2-butenyloxy, 3-butenyloxy, 2-methylallyloxy, ethynyloxy, 1-propynyloxy, 2-propynyloxy, and the like).

"Alkyl" represented by itself means a straight or branched, saturated or unsaturated, aliphatic radical having the number of carbon atoms indicated (e.g. (C_{1-6})alkyl includes methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, *tert*-butyl, vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methylallyl, ethynyl, 1-propynyl, 2-propynyl, and the like). Alkyl represented along with another radical (e.g. as in arylalkyl) means a straight or branched, saturated or unsaturated aliphatic divalent radical having the number of atoms indicated or when no atoms are indicated means a bond (e.g. (C_{6-12})aryl(C_{0-6})alkyl includes phenyl, benzyl, phenethyl, 1-phenylethyl 3-phenylpropyl, and the like).

"Alkylene", unless indicated otherwise, means a straight or branched, saturated or unsaturated, aliphatic, divalent radical having the number of carbon atoms indicated (e.g. (C_{1-6})alkylene includes methylene (-CH_2-), ethylene (-CH_2CH_2-), trimethylene (-$CH_2CH_2CH_2$-), 2-methyltrimethylene (-$CH_2CH(CH_3)CH_2$-), tetramethylene (-$CH_2CH_2CH_2CH_2$-), 2-butenylene (-CH_2CH=$CHCH_2$-), 2-methyltetramethylene (-$CH_2CH(CH_3)CH_2CH_2$-), pentamethylene (-$CH_2CH_2CH_2CH_2CH_2$-) and the like). For example, a group of Formula (a), wherein R^{11} is hydrogen and R^{12} taken together with R^9 forms optionally substituted trimethylene is depicted by the following illustration:



in which R is an optional hydroxy or oxo group and X^3 and R^1 are as defined in the Summary of the Invention for Formulae I and II.

"Alkylidene" means a straight or branched saturated or unsaturated, aliphatic, divalent radical having the number of carbon atoms indicated (e.g. (C_{1-6})alkylidene includes methylene (=CH_2), ethylidene (=$CHCH_3$), isopropylidene (=$C(CH_3)_2$), propylidene (=$CHCH_2CH_3$),